Background Document for the Food Advisory Committee

DETECTING SIGNALS FOR CHEMICAL HAZARDS OF CONCERN IN CFSAN-REGULATED PRODUCTS

September 2013

Detecting Signals for Chemical Hazards of Concern in CFSAN-Regulated Products

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September 23-24, 2013

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I. Introduction

The Center for Food Safety and Applied Nutrition (CFSAN or Center) is a science-based public health regulatory organization within the Foods and Veterinary Medicine Program of the Food and Drug Administration. CFSAN is charged with protecting and promoting the public health by ensuring that the United States' food supply (including dietary supplements) is safe, secure, and properly labeled, and that cosmetics are safe and properly labeled. The Center currently regulates approximately $417 billion worth of domestic food, $49 billion worth of imported foods, and over $60 billion worth of cosmetics sold across state lines.[1] Further, globalization, new technologies, and increased consumer demand for fresh and imported food products and for a greater variety of products is driving a need for new tools and standards to regulate a more complex and diverse food supply and cosmetic industry. Given these pressures and scope of its regulatory authority, CFSAN is committed to developing more effective and efficient processes within the Center to meet the challenges of emerging as well as existing food and cosmetic safety issues in the 21st century.

In an era of the 24-hour news cycle, issues surrounding the safety and security of the nation's food supply, dietary supplements, and cosmetics products is more scrutinized than ever. It is in the government's, industry's, and the public's interest to ensure that the flow of information is based on sound science and that regulators are attuned to and act upon critical hazards in order to protect and promote public health. A particular concern for CFSAN is ensuring that the Center is actively engaged in identifying chemical contaminants of concern in food and cosmetic products and is committed to taking regulatory action when necessary to ensure the safety of CFSAN-regulated products. With recent concerns surrounding chemicals such as Bisphenol A (BPA) and melamine in CFSAN-regulated products, CFSAN is seeking to develop and implement a pilot process within the Center that will proactively identify potential chemical contaminant hazards of concern. This process at CFSAN must encompass an action

[1] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofFoods/CFSAN/WhatWeDo/default.htm

plan to address these emerging chemical hazards and to communicate any relevant determinations to CFSAN leadership and stakeholders. With the continued advancements in scientific knowledge, CFSAN seeks to ensure that regulatory decisions remain grounded in sound science and that the public continues to rely on the safety and security of the nation's food, dietary supplement, and cosmetic products supplies.

CFSAN's Signals for Chemical Hazards Working Group at CFSAN prepared this background document for consideration by the Food Advisory Committee. The remainder of the document is dedicated to describing a proposed pilot process that CFSAN would be able to implement that will allow the Center to more proactively identify chemical contaminant hazards of concern in CFSAN-regulated products. The Working Group developed this proposed pilot process in consultation with various centers within FDA, other government agencies, CFSAN senior leadership, and several offices and active working groups at the Center. The focus of the process description below is primarily aimed at defining a chemical signal, considering what data sources should be considered by CFSAN as relevant indicators of potential chemical hazards, and determining what relevant criteria would warrant further investigation or regulatory action by CFSAN. A critical component is the recommended business process for implementation at the Center to ensure the flow of information reaches relevant decision-makers and offices within the Center to address emerging concerns. CFSAN seeks the input of the Food Advisory Committee on each of these key points in the proposed pilot process and on the system as a whole. Specific questions for the Food Advisory Committee are detailed in Appendix A. A flow diagram of the entire framework that is described below is in Appendix B.

II. A Framework for Chemical Signal Management System for CFSAN

A. Description of the System

Purpose of the System:

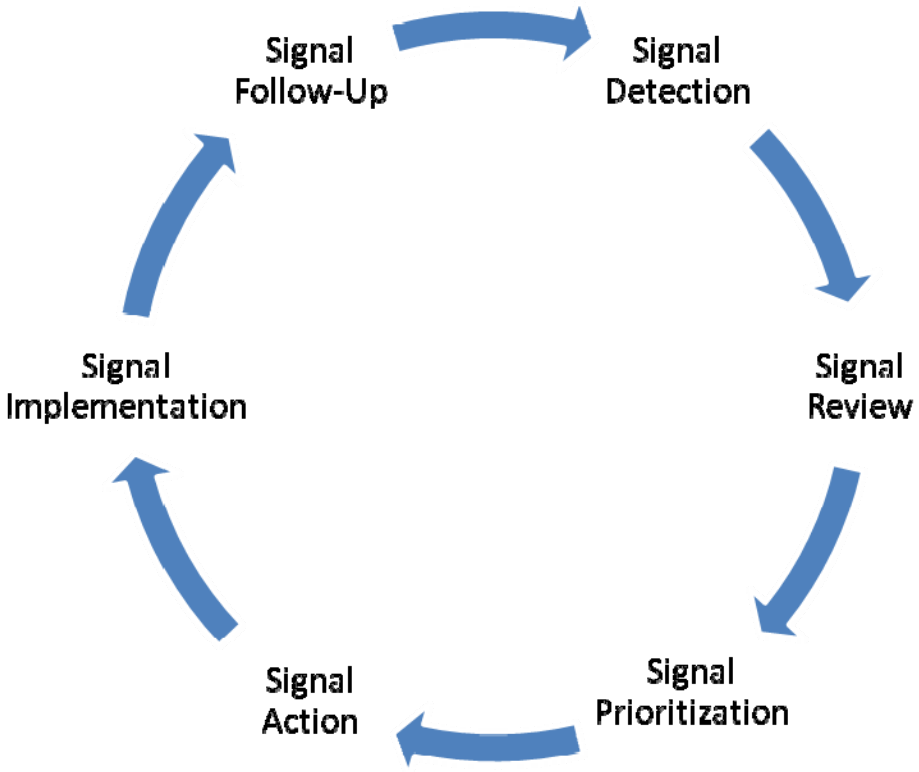
The purpose of the signal management system is to define and pilot a systematic and CFSAN-centric process that will: 1) identify and evaluate evidence of emerging chemical hazards or of newly recognized risks from known chemicals in food, dietary supplements, or cosmetics and 2) provide relevant information on an identified hazard across CFSAN to facilitate active communication and an appropriate response. The goal of signal management is to provide a dynamic system to better monitor and respond to emerging issues rather than to react after they occur.

Core Components of the Management System

1) Signal Detection/Identification
2) Signal Review and/ or Prioritization
3) Signal Action and Management
4) Signal Implementation and Follow-up

This system allows identified signals to constantly cycle through a review, management, and implementation process so that CFSAN can more effectively evaluate and respond to emerging chemical hazards in a coordinated and systematic approach.

Graphic 1: Illustration of the Cycle of Processing Signal Information in the Proposed Signal Management System



Definition of a Signal: The definition of a chemical signal is critical to implementation of a signal management system. CFSAN defines such a signal as:

1) Any information regarding a potential chemical contaminant hazard or reported adverse reaction in food, dietary supplements, or cosmetics that might be considered a risk or a perceived risk to public health; or

2) Any use of a chemical or combination of chemicals that may be used in a new way in foods, dietary supplements, cosmetics, food packaging, or processing that could significantly increase exposure; or

3) Any food, food packaging, dietary supplement, or cosmetic product or ingredients for which economic or supply conditions change substantially, leading to an increased probability of adulteration with chemicals (e.g., economically-motivated adulteration).

Adapted from Hauben and Aronson (Drug Safety 2009; 32(2):99-110)

Examples of Categories of Types of Signals That May be Considered:

- Adverse reactions suspected to arise from an unknown chemical in the food supply, dietary supplements, or cosmetics
- Known chemical that is or may be related to a newly reported adverse reaction or event
- Known chemical that is receiving new or renewed attention from a toxicological or risk assessment perspective
- Known chemicals that are receiving new or increased attention in the media or in legislative bodies
- Known chemicals that are newly regulated by other major international governmental entities
- Addition of new allergens to international regulations or an increased prevalence of an allergic response to a specific chemical or ingredient (e.g., Lupin has a similar structure to peanut allergens and can induce allergic reactions)
- Chemical that is known or reported to be contaminating a new food product or food commodity, dietary supplement, or cosmetic product
- Chemical that is not known to cause adverse reactions, but is considered unapproved for the use (e.g., unapproved colors or pesticides)
- Commodity that has undergone significant economic or supply changes and is vulnerable to adulteration by a chemical, or such changes would expose the public to a new chemical or toxin hazard
- Significantly increased exposure to a contaminant due to increased consumption of a particular food or product
- Newly detected chemical identified in a significant number of untargeted screening samples in a particular commodity
- New appearance, the increased frequency, or a significant change in quantities of chemical or chemicals in contaminant levels in FDA laboratory analyses from samples collected by compliance programs, field assignments, or the Total Diet Study

- New and emerging biotoxins from marine or fungal sources (e.g., new types of mycotoxins, new marine toxins)
- Significant changes in environmental conditions that could results in variations from normal or expected biotoxin distributions (e.g., algae blooms).

Source of a Signal: CFSAN will use a two-pronged approach to scan a wide range of data sources to facilitate the identification of potential signals. The first prong includes information from external data sources (e.g., literature searches, international risk assessments) that will come into a Signal Manager (the coordinator for the chemical signal detection system), as a monthly or quarterly report. Ideally, these reports will be done by contract with an information-gathering service. These reports will be evaluated for potential signals or trends by the Signal Manager (or a subject matter expert chosen by the Signal Manager). The second prong includes gathering information from internal data sources that are frequently used and monitored by CFSAN scientists, program officers, workgroups, or staff during their usual course of work. These internal data sources are used by cross-cutting research groups and can also be unique to specific offices within CFSAN. In addition, CFSAN program, research, and compliance staff possess broad expertise and knowledge as subject matter experts; therefore, any CFSAN employee will be able can submit a concern about a potential signal. Any potential concern could be submitted by an electronic signal report entry form through a data management and communication system (such as FDA's Traction or other similar tool) which will post in a Signal Manager's inbox. To provide clarification for the Food Advisory Committee, the internal sources are listed all together below and then an example is given for specific offices and the data sources that are used.

Identified Data Sources for Chemical Signals:

CFSAN uses a broad definition of data sources as it relates to this pilot approach and recognizes that there are many data sources that could be relevant to chemical signal detections. CFSAN anticipates that these data sources for signal detection will evolve over time as sources are re-evaluated for accuracy, the potential for signal identification, and the quality (and ease) of data collection. The recommended data sources include

databases or registries of information and products, but can also include information from employees, risk assessments, consumer or professional society opinions, or summary reports. Given that CFSAN is a regulatory agency, CFSAN will also consider program reviews, compliance actions, and information collected by the Office of Regulatory Affairs as data sources for chemical signal detection. Additional information regarding the data sources is listed in Appendix C. For the pilot process, CFSAN has identified these essential data sources:

External Sources:

1. Literature searches on global databases (either through the FDA library or contract with Reuters)
2. Information on research funding levels from RePORTER (NIH funding/grant databases)
3. Toxicology Data Network (TOXNET) Databases (e.g., Integrated Risk Information System, IRIS)
4. Agency for Toxic Substance and Disease Registry (ATSDR-CDC)
5. Other government agencies (e.g., EPA, CDC, USDA, specifically USDA Pesticide Data Program, NOAA's Mussel Watch Database, EPA Fish Consumption Advisories Database, EPA Discharge Monitoring Report Pollutant Loading Tool)
6. International Food Safety Chemical Liaison Group
7. International Food Safety Agencies and systems (e.g., European Food Safety Agency, RASFF - The Rapid Alert System for Food and Feed)
8. World Health Organization, Codex Alimentarius Committee, and related expert subject committees (e.g., JEFCA- the Joint FAO/WHO Expert Committee on Food Additives)
9. National Health and Nutrition Examination Survey (NHANES)
10. Consumer Advocacy and Industry Groups (e.g., Environmental Working Group, Center for Science in the Public Interest, National Resources Defense Council, Grocery Manufacturers Association, Food Marketing Institute)

Internal Sources:

1. Total Diet Study (TDS)
2. CFSAN research working groups (e.g., chemistry, toxicology, nanotechnology)
3. CFSAN Adverse Events Reporting Systems (CAERS) (e.g., dietary supplements)
4. Potential data sources through current contracts for pilot studies to evaluate economically-motivated adulteration (called FIDES) and to evaluate social media for adverse events or signals
5. Reportable Food Registry (RFR)
6. Compliance and Office of Regulatory Affairs--based Systems (to include FACTS, OASIS, MARCS, ORA Reporting, Analysis and Decision Support System, ORADSS)
7. MINTEL/GLADSON (market data).
8. Cosmetic Ingredient Review
9. International Cosmetic Ingredient Nomenclature
10. FDA Voluntary Cosmetic Registration Program

Offices Responsible for Sources:

To facilitate the implementation of this proposed detection system, it will be important that CFSAN offices be empowered and expected by virtue of their expertise and knowledge of certain data sources to submit potential chemical signals to the Signal Manager. For example, ***the Office of Analytics and Outreach (OAO)*** uses the following data sources in its work and would be expected to monitor them for potential signals:

- Outside contracts to evaluate social media and economically-motivated adulterations
- Evaluate having the CFSAN Consumer Studies Team conduct a focus group or expert elicitation study
- CAERS (CFSAN Adverse Events Reporting System)
- RFR (Reportable Food Registry)
- Total Diet Study

The ***Office of Food Safety*** would be expected to monitor the following sources for potential signals:

- Toxic Elements in Food and Foodware
- Radionuclides in Food Program
- Total Diet Study
- Pesticide and Industrial Chemicals in Food Monitoring Program
- Mycotoxins in Food--Domestic and Import Compliance Program
- Chemotherapeutics in Seafood Compliance Program
- Seafood Processor Inspection Program (mainly microbial, but also includes histamine testing)

Leveraging data sources already maintained and monitored by CFSAN offices and encouraging reporting of potential signals into a coordinated and centralized process will further enhance communication and decision-making across CFSAN programs and research. The combination of pursuing a two-prong approach with analyzed external data sources and leveraged internal data sources and expertise will allow for a comprehensive and centralized data flow for the chemical signal detection system.

B. The Process Description

Signal Detection and Identification

Given the short time frame and the need to develop a chemical signal detection system, CFSAN is proposing for this initial pilot phase to use an existing data reporting and managing system currently in use at FDA (Traction). The Traction system is an IT platform that allows FDA employees to easily communicate and share relevant information internally. The system provides a centralized site for users to post, email, and track information related to a particular issue and provides a historical record for action and communication. Traction has been used successfully by other FDA Centers for similar types of systems and Traction can be modified and used by CFSAN to pilot a signal management process. Using an existing system like Traction would eliminate, in this initial phase, the need to develop and implement a new database and management system. A longer term vision for CFSAN's signal management system (Phase 2)

includes developing a separate CFSAN data management and analysis system platform which would include an artificial neural network (see description in Appendix D).

The CFSAN **Signal Manager** is the focal point for the signal management system in that the signal manager is responsible for synthesizing and analyzing information related to signal detection and coordinating all communications and activities related to the management system. He or she is responsible for receiving the signals (including internal sources), the initial triage of prioritizing and gathering of additional information, leading the Signal Review Team, and the completion of the recommended actions for addressing the signal. The Signal Manager ensures tracking of the entire signal management process and the standardized documentation of signal evaluation and issues final reports.

Internal data sources are databases and data sources that are routinely used by CFSAN offices. In the course of their usual work or scientific duties, CFSAN employees may come across a signal (based on the definition and category, as described above) which they would submit to the Signal Manager via an electronic signal detection entry form in Traction (see Appendix E). Therefore, each CFSAN employee would be considered a signal detector. The form used to record this information will include such items as chemical name, food or cosmetic, reported event or detection (signal), name of person submitting the form, the program offices under which the signal would normally be handled. The form will thus provide contact information for the Signal Manager and establish an open record for that particular chemical or commodity.

The Signal Manager will also receive information and reports at regular monthly intervals from external sources such as FDA's contracts for social media searches or extensive scientific literature searches. Information from internal or external reports would be entered into a database as a new record or as part of an existing record. A system of weighting factors could be used to assign a level of importance to the signals reported for a given hazard or commodity, and thereby establish whether signals have reached a threshold for consideration at the next level of scrutiny. For example, a change in information about the toxicity or carcinogenicity of a chemical might be assigned a relatively high weighting factor, necessitating further attention on a

previously reported chemical. On the other hand, a non-peer reviewed report on the dangers of a well-known chemical might not add significantly to the overall signal record for that chemical. One important element of the process would involve the Signal Manager transferring information to the relevant CFSAN program office for timely comment, while at the same time maintaining an open record on the chemical or commodity. This would serve to enhance internal information flow and would allow the Signal Manager to determine whether the reported information was redundant or a new signal for the chemical or commodity in question.

During this pilot phase, there should be two full time positions available for CFSAN Signal Managers. The Signal Manager positions require informatics expertise (including expertise in database scanning, data-mining, data-organization and retrieval), and organizational and scientific expertise. This needed expertise may be difficult to find in one individual and the workload to operate, maintain, analyze, manage, and report on these chemical signals will require a minimum of two individuals to implement the centralized process. These managers could be trained by current managers in similar positions at another FDA Center.

The Signal Manager should have the ability and expertise to triage initial reports based on experience and overall knowledge of the signal detection system. For example, if a number of different reports had recently occurred on a given chemical, or if a single high-impact report appeared, the Signal Manager could deem the signal intensity had reached a level requiring additional consideration at another level. Thus, at any given time the Signal Manager would have options ranging from taking no action, leaving a record in active status, or facilitating the next step in the process.

The next step is the review of signal-related information by the **Signal Review Team** (expert review panel). The Signal Review Team will receive the signal-related information from the Signal Manager and meet on a monthly basis. The team will also meet on an ad-hoc basis as needed to address any new information received that is deemed to be of high significance. The team will be composed of a representative from each relevant office in CFSAN and will have the needed expertise to review and to prioritize the identified signals. The working meetings will include a presentation of the

chemical or commodity in question, the review of relevant materials (evidence for each reported signal, other background material), and recommended action (e.g., further evaluation, no actions needed, or suggestions for intervention(s)). These core members of the Signal Review Team should be experienced staff from each relevant office who are familiar with their office functions, policies, expertise, and have the ability to make decisions and assign other work. The core members will be expected to "champion" the process of signal management within their offices. The core Signal Review Team members will work with the Signal Manager to prioritize signals, interpret data, recommend additional subject matter experts, complete or assign additional research or background assignments by the appropriate office, develop and share action plans, and ensure senior management is aware of the potential signal. Other members could be added to the Signal Review Team such as ad hoc experts for a specific chemical, other interested CFSAN staff, and compliance or field personnel. These experts could also use their extensive scientific networks to solicit outside or international opinion.

Signal Review and/or Prioritization

The Signal Review Team will decide whether the chemical requires additional evaluation and research or is to be returned to the Signal Manager to maintain a record for continued monitoring. Because of limited resources, if a signal is not considered important in relation to regulatory, scientific, or public concerns, then the chemical/commodity signal is returned to an active record status (monitoring). However, if additional evaluation is required, the Signal Review Team will assign a "priority" category to the signal (e.g., "low" or " high") and decides on a plan for further review and assessment. If the signal for a chemical/commodity is not a high regulatory or research priority for CFSAN and does not appear to have a high public safety risk, then it will be designated as "low". Signals in the low category will receive limited additional review and the recommended action may be to continue monitoring the signal for additional data for a period of time. Another likely action in this circumstance would be to provide talking points or a briefing summary for future use by CFSAN. The evaluation and resulting information would be maintained in the signal management system and be

accessible for future use. Signals that are considered “high” priority will require additional research and documentation (e.g., systematic literature review, laboratory studies, or expert input) and, ultimately, appropriate actions and communication by CFSAN.

Potential Criteria Needed for Signal Review and/or Prioritization

The priority level assigned to a particular chemical signal will be based largely on the expertise of the Signal Manager and the Signal Review Team. However, the following are examples of signal scenarios that could result in a contaminant being assigned to the high priority level:

- The potential for contamination of multiple food products (e.g., fruit and juice)
- A product consumed in large quantities or consumed by a susceptible population (e.g., elderly or children)
- A significant increase in new research funding

CFSAN is requesting input to develop a decision tree based on criteria for review and prioritization that will help enhance a chemical signal management system and provide a set of criteria to distinguish between “background noise” and signals of concern. A decision tree will better clarify whether signals rise to a level of concern, continue through the system as either low or high priority (or other classifications such as low, medium, and high) and provide guidance to the Signal Manager and Signal Review Team.

Signal Action

Any signals receiving a “low” or “high” priority designations by the Signal Review Team will pass on to the next phase of the signal management process into the decision-making signal action phase.

Signal action is the process whereby the Signal Review Team’s recommendations will be passed on to a **Signal Management Team** that is composed of management-level representatives from each relevant office. The Signal Management Team will provide

feedback to the Signal Manager and Review Team as to the actions or mitigations recommended and provide recommendations for their implementations. In addition, the Signal Management Team will determine which office will be responsible for the implementation and completion of any recommended actions. If the signal, associated with a specific chemical/commodity, is considered critical and a high priority, then the Signal Manager and Review Team will prepare a brief summary that can be introduced by email or oral presentation to the CFSAN Management Council. This will provide senior leadership with rapid alerts about high priority and emerging signals, and will provide an opportunity for senior leadership to provide input and request specific actions or further review of the signal.

Signal Implementation

The next phase of the management system is Signal implementation or the implementation of the action plan. After discussions and recommendations by the offices, the Signal Review Team, Signal Management Team and, if applicable, the Management Council, a plan for dealing with the chemical/commodity at issue will be developed. Implementation actions might include specific targeted research to better evaluate a detected chemical, the establishment of coordinated research among agencies, meetings with industry, advice to the public, or even a compliance action. All recommendations and actions are to be documented with all reports and supporting materials maintained in a database (e.g., Traction).

Signal Follow-up

The Signal Manager will ensure any needed follow-up from the Signal Review Team or the Signal Management Team. Some signals may be monitored for a set period of time, while others may require that additional external sources are queried or specific research is implemented to address certain specific issues involving the Signal. Any additional information will be communicated and coordinated through relevant offices, Signal Manager, and Signal Review Teams.

A final report will be completed by the Signal Manager once the responsible offices complete the actions for the reported signal. This report will be accessible to all CFSAN staff via Traction and will be archived.

Example of Detected Chemical in the Signal Detection Process- To enhance clarity about the pilot system and to illustrate the flow of signal information, an example is provided below. A more detailed example will be given during the oral presentation to the Food Advisory Committee. The example illustrates signal information at different points in time coming from different sources regarding Pesticide X, and the way CFSAN might process the signal information using the proposed system.

III. Example of a signal coming through multiple sources:

Signal 1: Pesticide X (no tolerance in rice) is identified in imported rice in the Pesticides Compliance Program. The signal report is entered by Office of Compliance staff or Office of Food Safety case reviewer. No action is taken by Signal Manager except placement on list in regularly occurring report. Routine actions by the Agency to address the adulterated product are in progress.

Signal 2: Rapid Alert System for Food and Feed (international data reporting) report of Pesticide X in quinoa imported from France. This report is judged to be of low priority by the Signal Manager, and referred to the Signal Review Team for future review.

Signal 3: Office of Nutritional Labeling and Dietary Supplements staff reviewer files report of literature article identifying Pesticide X in herbal dietary supplements taken by nursing mothers. The report is judged as high priority because of the link to nursing mothers.

Follow up: The Signal Manager notices three occurrences of Pesticide X across different offices, and is able to identify Pesticide X usage as a broader problem across the CFSAN, illustrating one benefit of the centralized information sharing system. The Signal Manager, in conjunction with Signal Review Team and Signal Management Team initiates higher priority consideration of Pesticide X, and

provides action plans to individual offices and/or monitors individual office actions. Offices may have already proceeded with their own actions which illustrates the need for continual coordination and communication. This pilot process helps facilitate communication and coordination.

IV. Implementation and Outcome of Pilot Chemical Signal Detection Process

Implementation of this signal detection system will depend, in part, on the Food Advisory Committee's comments and suggestions. If this process is piloted, suggested actions for implementation are:

1. Communicate with all offices about the purpose and goals of the chemical signal detection working group.
2. Evaluate the use of Traction for CFSAN and customize for chemical signal detection.
3. Hire two Signal Managers and adequately train them. Training will also have to be provided for staff on Traction or other data management and networking systems that will be used.
4. Identify qualified members to serve on the Signal Review Team and the Signal Management Team.
5. Continue to develop other current CFSAN data management and analysis tools, e.g., artificial neural networking (Appendix D).

This pilot process will probably take six months to one year, with the goal to develop the CFSAN chemical signal detection system within two years.

V. Outcomes of Implementing a Chemical Signal Management System at CFSAN

1 .The development and implementation of a systematic chemical signals management process that is defined, has decision criteria, can be articulated to others, and will enhance communications about potential chemical hazards throughout CFSAN.

2. The rapid identification by CFSAN of chemicals in foods, food and color additives, dietary supplements, and cosmetics that may pose new or significantly increased risks to the public.

3. Senior level decision makers will be informed about new or changing risks associated with chemicals in foods, food and color additives, dietary supplements, and cosmetics allowing them to better facilitate strategies to address the risk.

4. The system will improve communications about signals from chemicals in foods, food and color additives, dietary supplements, and cosmetics within CFSAN.

5. The system will facilitate data-gathering in an effective process to better detect chemical signals by CFSAN.

Appendix A. Charge and Questions to the Food Advisory Committee

Center for Food Safety and Applied Nutrition September 23-24, 2013
Food Advisory Committee Meeting
Detection of Signals for Emerging Chemical Hazards

Charge and Questions

Charge: CFSAN intends to develop a framework or a systematic process to better enable the Center to recognize and evaluate evidence of emerging chemical hazards or newly recognized risks from known chemical hazards in food, dietary supplements, food and color additives, and cosmetics. CFSAN seeks to be more proactive in identifying and monitoring emerging issues rather than reacting to issues after they occur. The task before this Food Advisory Committee is to consider possible sources of information and data on chemical hazards and to provide input on how CFSAN might recognize and take advantage of incoming information and data. Such data can include reports of adverse reactions, both acute and chronic, provided such information can plausibly be linked to a chemical hazard. Specifically, there are several issues for which CFSAN would like a response from the committee:

Question 1: What are the sources of data and information on chemical hazards that might best identify emerging chemical hazards or newly recognized risks from known chemical hazards? Rank these sources of data or information in order of the expected value in identifying new or emerging chemical hazards.

Question 2: Are the signal definition and the categories of signal types clear, well-defined, and inclusive? Are the definition and categories sufficient to detect potential issues related to chemicals in foods, food and color additives, dietary supplements, and cosmetics? Are there other categories that should be included or others that should be deleted?

Question 3: Once a potential signal is identified, CFSAN recognizes the need for considering and weighting various factors in the review and prioritization of a signal, and subsequent action. What factors and weighting are most critical in moving an identified signal from the Signal Manager through the process to review? What factors and weighting are most critical in prioritizing a signal into particular categories ("low" versus "high")? What factors and weighting are most critical in deciding the follow-up and action on a signal?

Question 4: How should CFSAN conduct ongoing literature searches to capture new and emerging data on chemical hazards in published literature on foods, food and color additives, dietary supplements, and cosmetics as part of this detection system? What key words would be appropriate to search on? What journals are most valuable for this purpose?

Question 5: Are there specific web-based technologies or services which the FAC would recommend for generating effective broad literature searches and monthly reports? How frequently should these searches be done (e.g., monthly or at different frequencies)?

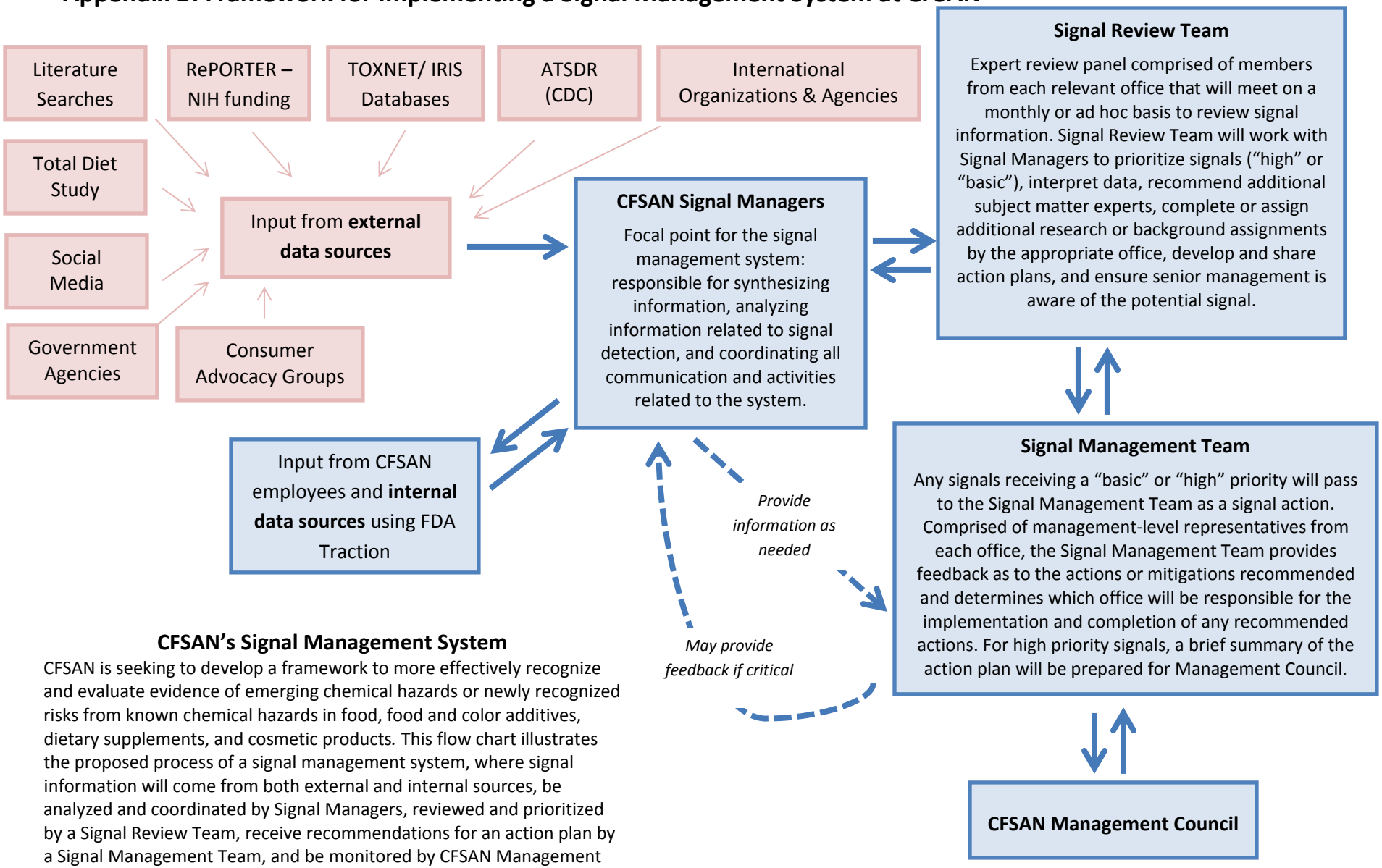
Question 6: Are social media tools available and refined enough to be of use in this area? Should CFSAN take advantage of current contracts with social media or are there other ways to obtain and analyze social media information? Would it be useful for this process?

Question 7: How should the various data for the chemical signal detection process be stored and managed? The current proposed system enables the data to be collected in one focal point, managed by two designated full-time employees, and stored on a designated server. Future plans involve a CFSAN specific data warehouse and analysis network. Is the current proposed system adequate for a pilot and for designing a long-term system? How should this repository be structured, who would have access, and how often should it be updated?

Question 8: What skill set should a signal manager have? Should he or she be an information management specialist, or should he or she have expertise in other scientific disciplines (e.g. chemistry, toxicology, epidemiology)?

Question 9: Does the signal review committee composition make sense? How often should it meet? Should there be any other types of committees considered for decision-making or to facilitate communication? Who should be included as members and what types of scientific disciplines should be included?

Appendix B: Framework for Implementing a Signal Management System at CFSAN



CFSAN's Signal Management System

CFSAN is seeking to develop a framework to more effectively recognize and evaluate evidence of emerging chemical hazards or newly recognized risks from known chemical hazards in food, food and color additives, dietary supplements, and cosmetic products. This flow chart illustrates the proposed process of a signal management system, where signal information will come from both external and internal sources, be analyzed and coordinated by Signal Managers, reviewed and prioritized by a Signal Review Team, receive recommendations for an action plan by a Signal Management Team, and be monitored by CFSAN Management Council.

APPENDIX C- Data Sources for Chemical Signal Detection with Descriptions

EXTERNAL DATA SOURCES

HHS Data Sources

NIH Funding Data

The relative levels of NIH research funding on the health effects associated with different chemical exposures is likely proportional to the levels of concern among scientists regarding the potential health risks of different chemicals. The NIH provides online access to a repository of information on NIH-funded research projects through its RePORTER (RePORT Expenditures and Results) module. The information found in RePORTER is drawn from several extant databases–eRA databases, Medline, PubMed Central, the NIH Intramural Database, and iEdison–using newly-formed linkages among these disparate data sources. The RePORTER database of research projects is updated weekly (addition of newly funded projects; revisions to prior awards). Costs shown in RePORTER are the total costs (direct and indirect costs) awarded in a single fiscal year. The RePORTER search form (accessible at http://projectreporter.nih.gov/reporter.cfm?tab3=3&def=1) provides many options for customized searches.

One type of simple search which can be conducted using the RePORTER search form is a "text" search of "Active Projects" (the default setting). Limiting the search to R01 equivalent and R03 Research Project Grants identifies specific focused projects only (i.e., excludes funding for other things like conferences, training, small business technology projects, education). Search results can be exported into an Excel spreadsheet. Included in the results are links to project-specific webpages which provide descriptive summary information for each project. This information could be used to eliminate projects that are not related to investigation of adverse health effects (for example, some of the projects for Arsenic are related to its use as a treatment for a rare form of leukemia). As an example of the relative funding levels for a few select chemicals of interest to FDA CFSAN, the table below provides the numbers of active projects and total NIH funding levels obtained from text searches conducted using the RePORTER module on May 30, 2013 for BPA, arsenic, aflatoxin, furan, perchlorate, and mercury

Chemical	Number of Projects	Total funding
BPA	40	13,406,714
Arsenic	65	22,781,554
Aflatoxin	17	4,700,059

Furan	14	4,633,976
Perchlorate	4	1,355,135
Mercury	36	12,798,493

For a pre-determined list of chemical additives and contaminants of interest, a ranking of the chemicals based on the funding levels obtained from the RePORTER database, along with a quarterly or biannual update of the ranking, would be one source of information which FDA could use to help inform decisions regarding future investigative or regulatory activities. The information is easy to obtain (obtaining search results manually takes only a few minutes per chemical) and the module is freely available online. The raw data from RePORTER are available for download at the NIH ExPORTER website (http://exporter.nih.gov/). Therefore the raw data could potentially be loaded into other data systems for automated data searches. Although the approach described above applies to a pre-determined list of chemicals, it is possible that the RePORTER database could be used to conduct searches to identify new chemicals of concern.

TOXNET

One example of the databases available through the FDA library is TOXNET (TOXicology Data NETwork). TOXNET is a group of databases covering chemicals and drugs, diseases and the environment, environmental health, occupational safety and health, poisoning, risk assessment and regulations, and toxicology (http://www.nlm.nih.gov/pubs/factsheets/toxnetfs.html; accessed on August 13, 2013). It is managed by the Toxicology and Environmental Health Information program in the Division of Specialized Information Services of the National Library of Medicine. Information in the TOXNET databases covers:

- Specific chemicals, mixtures, and products
- Chemical nomenclature
- Unknown chemicals
- Special toxic effects of chemicals in humans and/or animals
- Citations from the scientific literature

TOXNET databases include:

- IRIS (Integrated Risk Information System) - from the EPA
- ITER - A product of the Cincinnati based Toxicology Excellence for Risk Assessment, ITER presents chemical risk information from authoritative groups worldwide, including the U.S. Environmental Protection Agency, the U.S. Agency for Toxic Substances and Disease Registry, Health Canada, the Dutch National Institute of Public Health and the Environment, the International Agency for

Research on Cancer, as well as independent parties whose risk values have undergone peer review.

Agency for Toxic Substances and Disease Registry (ATSDR)

ATSDR is an agency within CDC that provides an informational portal of toxicological data for consumers, health professionals and scientists. The ATSDR database can be searched for chemical classification profiles, health and disease management guidance, toxicological profiles, and scientific assessments and consultations.

National Health and Nutrition Examination Survey (NHANES)

FDA utilizes information on dietary exposures of the U.S. population collected as part of the National Health and Nutrition Examination Survey (NHANES). NHANES is planned, implemented, and conducted by the National Center for Health Statistics, part of the CDC. NHANES is unique in that it combines personal interviews with standardized physical examinations and laboratory tests. The purpose of NHANES is to collect data about the health, nutritional status, and health behaviors of the non-institutionalized civilian resident population of the United States. Several surveys were conducted from 1959 to 1999. In 1999, NHANES became a continuous, ongoing annual survey. A continuous survey allowed content to change to meet emerging needs. Broad oversight for survey planning and content is provided through consultation with stakeholders, collaborating agencies, and other research partners. From 1999 through 2010, the dietary interview component obtained detailed dietary intake information from sample participants. Dietary intake data were used to estimate the types and amounts of foods and beverages consumed; to estimate intakes of energy, nutrients, and non-nutrient food components from foods and beverages; and to assess intake of water. The dietary interview comprised three sections: (a) dietary recall, (b) nutritional supplement and antacid use, and (c) post-recall. This component was conducted on sample participants of all ages (with proxy, if necessary). To allow for better estimates of usual nutrient intakes to assess diets in the U.S. population, two days of dietary intake data were collected for 2002-2010.

Other US Federal Government Agency Data Sources (USDA, EPA, NOAA)

USDA Pesticide Data Program

The USDA Pesticide Data Program (PDP) is a national pesticide residue database program. Through cooperation with State agriculture departments and other Federal agencies, PDP manages the collection, analysis, data entry, and reporting of pesticide residues on agricultural commodities in the U.S. food supply, with an emphasis on those commodities highly consumed by infants and children. PDP samples are collected by 11 participating states, which represent about 50 percent of the U.S. population

throughout all regions. Samples are collected close to the point of consumption. Collection at terminal markets and large chain store distribution centers allows the capture of sample identity data, takes into account pesticide degradation during transit and storage, and provides data on residues from postharvest applications of fungicides and growth regulators. Samples are randomly chosen without regard for commodity origin or variety. Samples reflect what is typically available to consumers throughout the year. PDP's statistically-reliable sampling protocol is designed to select random samples that best represent pesticide residues in the food supply to allow for realistic estimates of exposure to these chemicals. PDP maintains an electronic database which serves as a central repository for its residue monitoring data. The data captured and stored in the PDP database include product information, residue findings, and process control recoveries for each sample collected and analyzed, plus fortification results for each set of samples. Data for each calendar year are stored in a separate database structure, allowing for easier administration and reporting of data. Ad hoc queries and customized reports are generated in response to data requests from government agencies and the public sector. PDP calendar year databases are available for download from the PDP Web site. PDP has published Annual Summary reports to present program findings for calendar years 1991 through 2011.

NOAA Mussel Watch Program

Mussel Watch represents the longest running continuous contaminant monitoring program in U.S. coastal and Great Lakes waters, and analyzes chemical and biological contaminant trends in sediments and bivalve tissues collected at over 300 coastal sites. Parameters monitored include sediment and bivalve tissue chemistry for over 100 organic and inorganic contaminants. This project regularly quantifies PAHs, PCBs, DDTs and its metabolites, TBT and its metabolites, chlorinated pesticides and toxic trace elements. Mussel Watch supports NOAA ecosystem-based management through an integrated program of environmental monitoring, assessment, and research to describe the current status of pollution and to detect changes in the environmental quality of estuarine and coastal waters, including the status of contaminant concentrations around the continental U.S. coastline, as well as Alaska, Hawaii, and the Great Lakes, and Puerto Rico. Monitoring activities are designed to quantify and assess spatial and temporal trends in coastal contamination, and to provide a baseline to assess impacts of anthropogenic and natural events, including chemical spills, tropical storms, and hurricanes. Data can be obtained on a site-by-site basis using a web-based downloading tool, or the entire Mussel Watch Data Set can be obtained in ASCII file format for conversion to other formats or searching using other software tools. Other information from this program includes specific studies and publications in a number of areas, ranging from the effects of pesticide use to radionuclide accumulation.

EPA Fish Consumption Advisories

EPA Fish Consumption Advisories are a compendium of information on locally issued fish advisories and safe eating guidelines. When contaminant levels are unsafe, consumption advisories may recommend that people limit or avoid eating certain species of fish caught in certain places. Most advisories involve five primary contaminants: mercury, polychlorinated biphenyl (PCBs), chlordane, dioxins, and DDT, which can accumulate in sediments and make their way up the food chain to fish, sometimes increasing in concentration by several orders of magnitude. Fish consumption advisories are issued to help protect public health and may include recommendations to limit or avoid eating certain species of fish caught from specific local bodies of water due to chemical contamination. An advisory may be issued for the general public, including recreational and subsistence fishers, or it may be issued specifically for sensitive populations, such as pregnant women, nursing mothers, and children. An advisory for a specific body of water may cover more than one affected fish species or chemical contaminant. Information is provided to EPA by states, U.S. territories, Indian tribes, and local governments who issue fish consumption advisories and safe eating guidelines to inform people about the recommended level of consumption for fish caught in local waters. Information is available from the EPA web site directly or in the form of reports on specific pollutants and resultant advisories.

EPA Discharge Monitoring Report (DMR) Pollutant Loading Tool

The EPA Discharge Monitoring Report (DMR) Pollutant Loading Tool can be used to determine the nature of pollutants being discharged, the quantity, and where the discharges occur. The tool calculates pollutant loadings from permit and DMR data from EPA‘s Permit Compliance System (PCS) and Integrated Compliance Information System for the National Pollutant Discharge Elimination System (ICIS-NPDES). Data is available from 2007 onward. Pollutant loadings are presented as pounds per year and as toxic-weighted pounds per year to account for variations in toxicity among pollutants. The tool ranks dischargers, industries, and watersheds based on pollutant mass and toxicity, and presents “top ten” lists. The tool also includes wastewater pollutant discharge data from EPA’s Toxics Release Inventory (TRI). Users can search TRI data to find the facilities with the largest pollutant discharges to surface waters or sewage treatment plants. Users can also compare the DMR data search results against TRI data search results and vice versa. The information is accessible through a web-based tool or downloadable summary reports.

EPA Integrated Risk Information System (IRIS)

EPA's Integrated Risk Information System is a human health assessment program that evaluates information on health effects that may result from exposure to environmental contaminants. Through the IRIS Program, EPA provides science-based human health assessments to support the Agency’s regulatory activities. The IRIS database contains

information on more than 550 chemical substances containing information on human health effects that may result from exposure to various substances in the environment. The IRIS database is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD).

The heart of the IRIS database is its collection of searchable documents that describe the health effects of individual substances and that contain descriptive and quantitative information in the following categories:

- **Noncancer effects:** Oral reference doses and inhalation reference concentrations (RfDs and RfCs, respectively) for effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. In most instances, RfDs and RfCs are developed for the noncarcinogenic effects of substances.

- **Cancer effects:** Descriptors that characterize the weight of evidence for human carcinogenicity, oral slope factors, and oral and inhalation unit risks for carcinogenic effects. Where a nonlinear mode of action is established, RfD and RfC values may be used.

International Data Sources

International Food Chemical Safety Liaison Group

The International Food Chemical Safety Liaison Group (IFCSLG) is a working group with representatives from various international food standards agencies with the goal of enhancing information sharing between these agencies. The group provides an informal forum for government organizations involved in the risk assessment, risk management, and/or communication of food chemical safety to discuss and collaborate on issues of mutual interest. Membership of the IFCSLG currently comprises representatives from the United Kingdom, Canada, United States, Japan, New Zealand, the European Food Safety Authority, the European Commission, New Zealand, and France.

The activities of the IFCSLG focus on:

- Current research and data gathering efforts associated with selected chemicals in foods;
- Various approaches of risk assessment, the development of risk management options, as well as risk communication;
- Guidance to offer to consumers and to the food industry related to the occurrence of such chemicals in food;
- Avoidance of duplication of data generation activities between members;
- Development of a collaborative framework; and

- Creation of synergies among members to fill data gaps and develop data required for the assessment of chemicals in foods.

The IFCSLG has conference call updates every four months to share results of environmental scans, to share priority setting/emerging issues for each fiscal year, and to share draft press releases and data postings. There are also semi-annually meetings as agreed upon by Members, drawing on opportunities of meetings and gatherings during international events (e.g., Codex Committee for Contaminants in Food (CCCF)).

European Food Safety Agency (EFSA)

The European Food Safety Agency (EFSA) was created in 2002 by the European Union to provide an independent source of scientific advice and communication on risks associated with the food chain. In collaboration with national authorities and open consultation with stakeholders, EFSA provides independent scientific advice and clear communication on existing and emerging risks in regards to food and feed safety. EFSA produces scientific opinions and advice to provide a sound foundation for European policies and legislation and to support the European Commission, European Parliament, and EU Member States in taking effective and timely risk management decisions. EFSA also produces extensive risk assessment and guidance documents about emerging food safety issues that can be used as a signal and for background information. The risk assessments are often qualitative, not quantitative. The risk assessments are often large documents, and may not reflect U.S. policy.

The Rapid Alert System for Food and Feed (RASFF)

RASFF is an IT tool that facilitates the exchange of information related to food safety amongst European countries. It was started in 1979 to help notify European food agencies about emerging risks in the food supply. In 2012, 3516 notifications were sent through the system, with 5281 follow-up communications. Some examples of notifications in 2012 that might be considered as signals from this system (in addition to numerous microbiological alerts, which are not listed here) include:

1. High histamine levels in imported seafood products
2. Undeclared milk allergens in chocolate; undeclared peanut in chocolate; (100-120 notifications per year for allergens)
3. Undeclared sulfites
4. Unauthorized additives and vet drugs
5. Methanol in on tap spirits
6. DSP toxins in mussels
7. Ciguatera in snapper
8. Mycotoxins (525 reports); ochratoxin as an emerging mycotoxin problem
9. Pesticide residues (by class)
10. Industrial contaminants and heavy metals

In 2012, RASFF alerted members to methanol contamination of Czech spirits, which resulted in 36 deaths. In 2012, RASFF also helped disseminate information from Ireland that 100% beef products were adulterated with horsemeat, leading to significant traceback and product withdrawal throughout Europe. The process of providing information in the system is becoming standardized through a web portal. The types of reports include alerts (in which a product with a risk has been exported to other countries) and notifications, where risks are localized to the reporting country. Information consists of a notification form and accompanying supporting documents. The information generally includes the notifying country, the type of notification, the nature of the risk and the types of products. The information from RASFF will be available to non-RASFF members and FDA should have access to this information through the agreements that are being developed through the Office of International programs.

RASFF could serve as a source to the signals detection group that could highlight risks other countries are reporting. These would not necessarily be issues that we would see directly, since we might not be importing from those countries. However, particular value might be derived by the collecting and categorizing the data from RASFF to identify patterns; these patterns might suggest areas that the FDA should consider. For example, in the next year, the FDA will do a small assignment focusing on undeclared milk allergens in imported chocolate products; the observation of several years of such reports from European sources might have provided impetus to do this assignment earlier.

Codex Alimentarius Comission/Codex Committee on Contaminants in Food

The Codex Alimentarius Commission (CAC), established by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) in 1963, develops harmonized international food standards, guidelines and codes of practice to protect the health of the consumers and ensure fair practices in the food trade. The Commission also promotes coordination of all food standards work undertaken by international governmental and non-governmental organizations. Commission work is undertaken by various committees. The Codex Committee on Contaminants in Food, or CCCF, focuses on contaminants in food and feed. The terms of reference of the Committee are (a) to establish or endorse permitted maximum levels (MLs) or guideline levels for contaminants and naturally occurring toxicants in food and feed; (b) to prepare priority lists of contaminants and naturally occurring toxicants for risk assessment by the Joint FAO/WHO Expert Committee on Food Additives (JECFA); (c) to consider methods of analysis and sampling for the determination of contaminants and naturally occurring toxicants in food and feed; (d) to consider and elaborate standards or codes of practice for related subjects; and (e) to consider other matters assigned to it by the Commission in relation to contaminants and naturally occurring toxicants in food and feed.

CCCF maintains the General Standard for Contaminants and Toxins in Food and Feed (GSCTFF), a document that contains the main principles which are recommended by the CAC in dealing with contaminants and toxins in food and feed, and lists the MLs and associated sampling plans of contaminants and natural toxicants in food and feed which are recommended by the CAC to be applied to commodities moving in international trade. The Committee also holds yearly meetings to review draft MLs, codes of practice, and discussion papers. Information on emerging chemicals or chemicals experiencing renewed interest is likely to come from nominations for new work (e.g., new MLs or codes of practice) by member countries, as well as nominations to the JECFA priority list of contaminants and naturally occurring toxicants for risk assessment. These nominations for new work and inclusion in JECFA's priority list could be a signal of an emerging chemical contaminant that CFSAN could investigate.

Although not officially part of Codex, the Joint FAO/WHO meetings on Pesticide Residues (JMPR) is similar to JECFA in that it is a committee of experts. These joint meetings provide independent scientific advice on pesticide residues. FAO and WHO maintain separate websites highlighting the work of JMPR and could be a source of emerging chemical hazards.

Consumer Advisory Groups, Consumer Advocacy Groups, and Industry Trade Groups

These organizations represent consumers or industry/market customers to provide a coherent and organized mission of educating and/ or lobbying for the protection of consumers or industry interests. These organizations often drive the public perception of a risk, whether founded or unfounded, in public media and forums. These organizations often have websites with regularly updated and prioritized lists of their chemicals of concern. These lists can be monitored for information related to a potential signal such as new chemicals of concern, information driving the risk perception, and the types of media actions or public outreach.

INTERNAL DATA SOURCES (FDA)

Literature Searches either through the FDA Library Databases or an External Contract

The FDA library offers access to a number of global bibliographic databases that are a potential source of information on chemical contaminant issues. The databases can be set up to run customized searches of multiple terms. The frequency of searches is up to the user. The databases are bibliographic, so typical formats would include citations, abstracts, and descriptors. An example of two searches of 24 databases in food science

and chemical literature is shown in the table below, one covering approximately two months and one covering approximately 6 months. The number of abstracts could be large and burdensome depending on the number of chemicals that are concluded in the search. Review of searches would be done by FDA "expert" employees in order to eliminate literature that is not related to investigation of adverse health effects. For example, a search on Acrylamide:

May-June 2013

Items	File
4	2: INSPEC_1898-2013/Jun W3
22	34: SciSearch(R) Cited Ref Sci_1990-2013/Jun W4
3	305: Analytical Abstracts_1980-2013/Apr W3
1	317: Chemical Safety NewsBase_1981-2013/Jun
8	354: Ei EnCompassLit(TM)_1965-2013/Jun W4

January-June 2013

Items	File
3	5: Biosis Previews(R)_1926-2013/Jun W3
15	2: INSPEC_1898-2013/Jun W3
113	34: SciSearch(R) Cited Ref Sci_1990-2013/Jun W4
2	302: INDEX CHEMICUS_1993-201328
39	305: Analytical Abstracts_1980-2013/Apr W3
3	317: Chemical Safety NewsBase_1981-2013/Jun
22	354: Ei EnCompassLit(TM)_1965-2013/Jun W4

Alerts on a particular topic or chemical compound can be set up in almost all individual databases. A general approach recommended by the library is to use a resource that is broad in scope like Web of Knowledge (includes Web of Science, Biological Abstracts, and Medline), coupled with alerts in Food Science & Technology and SciFinder, which provide access to Chemical Abstracts. Another option is for FDA to contract with a literature scanning service such as Reuters. Reuters or similar companies will provide searches of these databases at regular intervals and provide comprehensive reports.

The following databases are available through the FDA library:

- AGRICOLA AGRIS

- BIOSIS Previews® (1926-present) CAB ABSTRACTS
- FSTA®
- Federal Research in Progress (FEDRIP) Foodline®: SCIENCE
- Foods Adlibra™
- General Science Abstracts
- Inside Conferences
- NTIS -National Technical Information Service
- PASCAL
- Wilson Applied Science & Technology Abstracts
- PubMed
- Web of Knowledge
- Em base
- Food Safety & Technology Abstracts (FSTA) Google Scholar
- Google Alerts
- Web of Knowledge
- Twitter
- TOXNET
- SciFinder

Total Diet Study

The Total Diet Study (TDS), sometimes called the market basket study, is an ongoing FDA program that determines levels of various contaminants and nutrients in foods. From this information, dietary intakes of those analytes by the U.S. population can be estimated. Since its inception in 1961 as a program to monitor for radioactive contamination of foods, the TDS has grown to encompass additional analytes, including pesticide residues, industrial chemicals, and toxic and nutrient elements. The primary purposes of the study are to monitor levels of these analytes in the U.S. food supply and to estimate their dietary intakes by selected age-gender groups in the U.S. population. This information also provides a tool for supporting regulatory actions and for tracking the impact of the regulations over time. TDS results have identified levels of contaminants or nutrients that were outside the normal range, or residues of pesticides that were not registered for use in the U.S. If the levels exceed the normal range, this information is identified and communicated to CFSAN; however, the time from sampling to analysis and identification can take months to a year. A beneficial feature of TDS is if a level that exceeds the normal range is identified, the TDS database can be further examined to determine additional sources of a contaminant and background exposure as well as to modify future sampling procedures to better understand dietary exposure to a particular contaminant.

Working and Coordinating Groups

In addition to input on signal detection from CFSAN employees, the Center also has a number of working groups and technical steering committees that drive the strategic planning process for science and research at CFSAN. In addition, the groups and committees facilitate more effective cooperation on methods development and validation across CFSAN, CVM, and ORA. These working groups and committees meet on a regular basis and are composed of research and regulatory staff charged with identifying specific research needs that are important to the regulatory and public health mission of the center. Through routine dialogue and sharing information about current research and emerging regulatory needs, these committees could easily be asked to discuss and provide intelligence on chemicals of concerns. Gaining potential signal information through these existing science and research coordination groups also allows CFSAN to also receive input from CVM and ORA in the detection process. These existing working groups at the center upon which CFSAN scientists and managers already serve could enhance the "signals detection" network.

CFSAN Adverse Events Reporting System (CAERS)

CAERS collects voluntary reports of post-market serious and other adverse events citing foods, dietary supplements, and cosmetics from consumers, health professionals, government agencies, and others. CAERS receives reports through MedWatch, emails, telephone calls, faxes, letters, and electronic transfers from the Office of Regulatory Affairs (ORA) District Offices' Field Accomplishments and Compliance Tracking System (known as FACTS). CAERS also collects mandatory dietary supplement reports of postmarket serious adverse events, defined in Public Law 109-462 as congenital anomalies or birth defects, deaths, persistent or significant disabilities or incapacities, inpatient hospitalizations, life-threatening conditions, and events requiring medical or surgical intervention to prevent such outcomes based on reasonable medical judgment, from manufacturers, packers, and distributors of dietary supplements. CFSAN staff conducts data mining of the database to identify adverse health event signals which may be related to specific products. Additional investigation of such signals can identify products of concern, occasionally with specific chemicals or ingredients in the products being implicated.

CAERS for Dietary Supplements

The two databases for assessing signals with dietary ingredients in dietary supplements include CAERS and safety data in NDI notifications. FDA's adverse event reporting system for dietary supplements includes (1) detecting signals in voluntarily submitted adverse events, (2) detecting signals in mandatory serious adverse event reports, (3) assessment of signals for possible public health concern, and (4) taking appropriate

safety actions based on its assessment. An adverse event is an incident of illness or injury that may be associated with a product or ingredient.
When a signal of a possible health problem is generated from the adverse event reporting system, FDA assesses whether it is an actual public health problem warranting attention. FDA assesses these signals by reviewing scientific literature, consulting with experts, reviewing clinical data, conducting its own laboratory tests, and/or commissioning studies. If FDA confirms that a public health problem exists it can take a range of safety actions, ranging from the issue of warnings to consumers and health professionals, import alerts, requesting product recalls, administrative detention, product seizure, and injunction of the firm.

New Dietary Ingredient Notification Database

The New Dietary Ingredient notification database can also be mined for signals. An example is consumption of ECGCs at high levels in dietary supplements. One notification suggested a possible mechanism for ECGCs inducing iron-deficiency anemia in consumers through iron chelation. While the data suggesting iron-deficiency anemia was at consumption levels exceeding the recommended conditions of use or apparent in animal studies after chronic consumption, the signal could be used to monitor other finished dietary supplement products containing that dietary ingredient.

Social Media Sources

FDA has two related projects that are gathering social media information. Both projects are through the Office of Analytics and Outreach. The first is a contract with Arizona State University (G. Gonzalez) to mine social media for adverse reactions to nutritional products. This includes Twitter, Amazon, and Daily Strength. The second includes a contract with Epidemico, a health data collection and analytics company, which provides a mobile app and social media monitoring for infectious diseases. The current contract with FDA is being piloted as a way to collect information for Medwatch. Medwatch is a system to detect adverse reactions for CDER, CBER, and CDRH. CFSAN could potentially add a module for chemical signal detection through this contract with Epidemico.

Social media pilot study

In the future, data mining of social media may be useful as a source of information regarding chemical issues that are of concern to the public. Currently a pilot study is being conducted on surveillance of adverse event reports through natural language processing of online user-generated postings about CFSAN-regulated products using software tools. This research involves identifying publically available data sources that contain sufficient numbers of user generated adverse event reports to allow statistical validation of the technique. The project will create and use software tools to identify

adverse event postings, collect and categorize them against a standard medical vocabulary such as MedDRA in a structured way, using natural language processing tools for extraction, classification, and sentiment analysis. The data generated by this process will allow standard analytical methods of signal extraction to be applied. The project will evaluate the sensitivity and specificity of the methods using case studies of known product-event pairs. The researcher will evaluate the systems developed on their ability to recognize adverse event reports; map them to standard terminology, and use for epidemiological and signal detection analysis.

National Center for Food Protection and Defense (NCFPD) – Focused Integration of Data for Early Signals (FIDES)

The National Center for Food Protection and Defense at the University of Minnesota has several ongoing projects related to prevention of economically-motivated adulteration (EMA). One of these is FIDES – Focused Integration of Data for Early Signals. The goal of this project is to provide a comprehensive systematic process for monitoring potential food systems risks and identifying adverse food events through data fusion and analytics (http://www.ncafdo.org/default/assets/File/Amy%20Kircher%202012-10-18%20NCAFDO%20EMA%20FIDES.pdf; accessed on July 30, 2013). The initial FIDES project work involved development of a technique for monitoring import data (from Customs and Border Protection) for anomalies in shipment quantities. Evaluation of this data by NCFPD demonstrated significant deviations from baseline levels/sources for shipments of wheat gluten that preceded the 2007 melamine-contaminated pet food incident. In the future NCFPD envisions ongoing automated surveillance to detect such signals by FIDES. When detected, such signals would then be evaluated by a group of internal and external experts. The results of this evaluation could then be used to identify possible interventions for consideration when the possibility of an EMA event occurring was deemed to be high. NCFPD is in the process of identifying additional data sources (e.g., commodity prices) to integrate into FIDES as potential indicators of EMA risk.

Reportable Food Registry (RFR)

The RFR (established by Section 1005 of the Food and Drug Administration Amendments Act of 2007) requires a responsible party to file a report through the RFR electronic portal when there is a reasonable probability that the use of, or exposure to, an article of food will cause serious adverse health consequences or death to humans or animals. Such foods are “Reportable Foods.”

“Responsible party” is defined as the person who submits the registration information to FDA for a food facility that manufactures, processes, packs, or holds food for human or

animal consumption in the United States. Responsible parties must report as soon as practicable, but in no case later than 24 hours after a responsible party determines that an article of food is a reportable food. Federal, state, and local public health officials may also use the portal to voluntarily report information that may come to them about reportable foods.
(http://www.fda.gov/downloads/Food/ComplianceEnforcement/UCM181885.pdf; accessed on July 18, 2013)

Usually an issue identified through the RFR is addressed in a straightforward manner such as a product recall and identification/correction of the cause of the problem (e.g., inadequate allergen warning on a label). However, on occasion larger issues are brought to light through the RFR. Examples include: (1) a false positive peanut allergen report for gum arabic which led to recognition of problem with a laboratory analysis method that was likely causing both false positives and false negatives; and (2) two reports of life-threatening allergic reactions to unidentified milk in chocolate bars, which led to recognition of one supplier with a production line contamination issue.

Programmatic Driven Data Sources

ORA's Workgroup for Economic Motivated Adulteration (WEMA)
This group meets once a month to discuss issues that are of concern across the agency in the area of economically-motivated adulteration (EMA). There may or may not be a sub-group devoted to foods issues in the future, but for the time being, CFSAN's Office of Regulatory Science sends a couple of scientists and managers to attend these meetings. CFSAN could request that a few minutes of each meeting be devoted to the question of what is on the radar screen in the agency and feed this information back to CFSAN via the attendees. CFSAN's own version of WEMA meets once a month or once a quarter and includes members from ORA. Information about potential emerging concerns is occasionally discussed and concerns could be fed to the signal detection system.

Summary of OFAS Food Label and Market Share Databases
GLADSON Nutrition Database
The Gladson Nutrition Database covers over 90% of all major product categories in industry. It provides syndicated consumer packaged goods, product images and nutrition information with UPC codes. The Office of Food Additive Safety (OFAS) uses this database to identify ingredients in packaged food products. The UPC codes captured in this database also can be merged with Nielsen market share data to generate sales weighted mean nutrient values for food categories. A few limitations with this data source include that some nutrient values are not available for certain

Nielsen-derived top-selling food items, and the database currently does not facilitate a way to readily monitor product reformulations over time.

MINTEL Databases

Global New Products Database (GNPD)
This database covers product innovation and retail success in the consumer packaged goods market and provides product records containing up to 80 fields, which include label data (nutrition information and full ingredient list), bar codes (including UPC codes), positioning claim information, product images, pricing information and data on product launch success from Information Resources, Inc. (IRI). Data are available from 1996 forward for 49 countries in 32 food categories. These data can be used to track the launch of new products within categories of interest and to drill down into the ingredients, nutritional information and positioning claims featured within these products, as well as allow for OFAS to merge UPCs from this database with Nielsen market share data to generate sales weighted mean nutrient values for food categories. However, this database contains data on fewer products than Gladson Nutrition Database and provides nutrition information for only a limited number of U.S. food products (missing data). Another limitation is that the database currently does not facilitate a way to readily monitor product reformulations over time.

Mintel Oxygen
This database offers comprehensive qualitative and quantitative consumer and market research reports covering US, UK, and European consumer markets. It provides insight into market drivers, market size and trends, market segmentation, retail distribution, advertising and promotions, consumer attitudes and spending habits, and a five-year future forecast. Mintel Oxygen captures background information, trends, and consumer attitudes well.

Mintel GMN (Global Market Navigator)
Mintel GMN provides market size, market share, and forecast data for thousands of consumer goods worldwide (47 countries, 18 industries). GMN generates trend reports on topics including U.S. restaurants, fast food, and take-away coffee shops, providing information on market segmentations and limited market shares by volume and by value. The data can be used to check market conditions in an unfamiliar industry, region, or country or compare performance of similar categories to identify threats, risks and opportunities (i.e., comparing energy drinks to juice to flavored water). The database provides key background information, trends, and consumer attitudes data, as well as information on restaurant segments and market share. Such information was

compared to data from Technomic in developing a restaurant internal database for sodium.

Mintel Menu Insights

This database provides information on menu trends, market insights, and actual menus from the restaurants under Mintel's surveillance (580 restaurants in the US with over 2,400 menus -- 355 Chain Restaurants, 150 Innovative Independent Restaurants, 50 Top Chef Owned Restaurants, 25 Beverage Operations, and 50 Regional Chains). Trends tracked include top menu item cuisine type, top menu item dishes, average menu item price per restaurant, among others. Data on menu items, top restaurant chains based on number of outlets, market share, and insight on different restaurant segments was considered in developing an internal database for sodium, however limited information on fast food restaurant market share is found in this database.

Mintel Inspire

Mintel Inspire is a global trends tool that provides relevant, strategic, evidence-based insights that enable understanding as to why a shift in consumer behavior is happening and what implications exist. Trends are analyzed by industry, demographic, and theme, with content updated regularly through trend observations and expert blogs. OFAS uses this database to understand general trends and consumer behavior

FoodEssentials LabelBase

FoodEssential LabelBase is a custom online system for accessing both Mintel and Gladson data via powerful keyword, ingredient, nutrient, allergen, additive queries and searches. All data are exportable for further research. This enables OFAS to search for and export nutrition, allergen, and other label data captured in Mintel and Gladson for further analysis (e.g., filter food categories, merge UPCs with Nielsen data) An advantage of this database is that data are continually being updated from Gladson and Mintel, however there are still a lot a data that needs to be added. In addition, search features in this system have not always been optimal, and data exports have not always been thorough and have had to resort to pulling data from Mintel and Gladson individually. Other limitations include the system is not always up and running as it should be, and the database currently does not facilitate a way to readily monitor product reformulations over time.

AC Nielsen Scantrack

Nielsen Scantrack examines business trends by product (including private-labels), category, or market using retailer scanner-based sales and gathers information from tens of thousands of retail outlets. OFAS uses Nielsen Scantrack to merge data with Gladson and Mintel nutrition data to calculate sales-weighted averages for food

categories, as well as identify companies and brands for top selling food products. A few limitations include the system is not user-friendly when working with different categories, and there may be a lag in updates with certain foods.

Cosmetic Ingredient Review (CIR)

The Cosmetic Ingredient Review was established in 1976 by the Personal Care Products Council with support of the FDA and the Consumer Federation of America. The CIR Expert Panel is an independent, industry-funded panel of medical, toxicological, and chemistry experts that meets quarterly to conduct safety assessments of cosmetic ingredients.

Personal Care Products Council

The Personal Care Products Council (formerly the Cosmetic, Toiletry and Fragrance Association) is the leading national trade association for the cosmetic and personal care products industry and represents the most innovative names in cosmetics. The council provides the voice of member companies on scientific, legal, regulatory, legislative and international issues for the personal care product industry. The Council is an important source of information for and about the industry, consumer safety, and continued access to new and innovative products.

International Cosmetic Ingredient Nomenclature (INCI)

The INC was established by the Personal Care Products Council. The INC develops ingredient labeling names for the International Cosmetic Ingredient Dictionary and Handbook. The committee evaluates ingredient submissions and petitions for cosmetic ingredient names and monographs..

Appendix D for Pilot Phase 2: This involves CFSAN developing a specific data management and analysis system that would include bioinformatics and artificial neural networks. This phase will develop a system to manage and analyze for data including foods, food and color additives, dietary supplements, and cosmetics.

This is a brief summary of proposed efforts within CFSAN to develop a data management and analysis system to meet specific research and regulatory needs. These efforts are in initial development, have not been tested, and will take another 12-24 months to pilot and implement. These data management, storage, and analysis systems could be adapted for the chemical signal detection system. As opposed to the manual identification proposed for the pilot, the CFSAN system will develop and implement software that focuses on bio-informatics and artificial neural networks. Some of the major advantages of artificial neural networks are the ability to analyze wide arrays of data and databases, examining complex or multivariate correlations, and the ability to define criteria post hoc. The ANN artificial neural network can be a stand-alone system, or can be used in tandem with the previously described signal detection system, especially in defining, refining, or validating criteria for identifying signals.

Signal Detection and Prediction System for Food Safety within CFSAN

Benefit

The signal detection/prediction system described below incorporates recent advances in systems technology for automated analysis of expansive sets of data with minimal resource and personnel requirements. The system is self-correcting with learning capabilities to provide refined prediction strategies with the addition of new data. The ability for the system to incorporate and utilize various unrelated sources and types of data provide additional benefit and application to various targets of interest.

Introduction

The ability to detect signals as an approach to predict an impending food safety issue caused by chemical or microbial contamination has been particularly difficult. This is partly because the factors that are indicative of such events are distributed across multiple databases. Individual events within each database have proven inadequate in predicting potential chemical or microbial hazards in the food supply. To efficiently detect such signals; we will need to design a system that is capable of collating information across different databases and recognizing the emergence of a pattern or patterns that consistently predict the event of interest. As is often the case, the target problem may be an unknown (e.g. new contamination incidents). Additionally, the particular pattern of events that predicts the target incident may not be known *a priori*. These factors reduce the utility of traditional regression models in predicting such events. To adequately analyze such information, one will need a system that is capable of modeling complex nonlinear relationships, has excellent fault tolerance, is fast, highly scalable, and capable of parallel processing. The system should also be capable of self-organizing to recognize the emergence of previously unknown patterns. A modeling approach that fulfills all these requirements is the implementation of an Artificial Neural Network (ANN).

Artificial Neural Networks

Artificial Neural Network is a machine learning method inspired by the idea of imitating the human brain. Each neuron in the human brain is capable of very simple computations; however, when the neurons are inter-connected into a network, the brain is capable of performing complex task such as speech and facial recognition with amazing speed and accuracy. Artificial neural networks attempt to harness this concept of distributed parallel processing to solve complex problems such as pattern recognition and Quantitative Structure Activity Relationship problems. ANN's are built as an interconnection of nodes, where each node represents a neuron. ANN's have three important components; node character, network topology, and learning rules. The node character defines how signals are processed by the node. This includes the number of inputs and outputs associated with the node, the weights associated with each input and output and the activation function. Network topology refers to the way in which the

nodes are organized and connected to each other. The learning rules define how weights for each node are initialized and adjusted. There are two major categories of learning that would be implemented in the proposed Signal Detection System (SiDS); supervised and unsupervised learning.

Supervised Learning

In supervised learning, training inputs (independent variables) and targets (dependent variables) are provided to the system. The targets can be chemicals or events such as recalls, outbreaks, regulatory action, congressional requests, research study applications or funding, social media reports, etc. The data from the input databases goes through a preprocessing stage for feature extraction. Feature extraction reduces the number of parameters that the ANN has to process while still maintaining the integrity of the data. The ANN is then allowed to analyze the data to find inputs, weights, and the optimum network configuration that can systematically predict the targets. During the training, the weights are adjusted to reduce the error (strengthen the correlations) between the network output (identification of a signal) and the data sources.

We will investigate using Bayesian regularization of the network instead of the standard error-back propagation in optimizing the weights and configuration of the network. Bayesian regularized neural networks are advantageous because they are robust and reduce the need for lengthy cross-validation. They also minimize the tendency to overfit models because training is done on a number of effective network parameters and/or weights, turning off those that are not relevant. This can be considered a method of pruning the network resulting into the most parsimonious network necessary for efficient prediction of target values. As part of the initial development and proof-of-concept in training and testing the network, data from our current databases will be divided into three. The first dataset will be used to train the network, the second dataset will be used to validate and refine the network. After the network is refined, the network weights and topology are fixed. The third dataset will then be used to test the performance of the trained network. Possible network models for use include the multilayer perceptron and the counter-propagation ANN. The actual network topology to be used will be

determined experimentally (see Fig. 1 for a schematic of an ANN topology and processing stages).

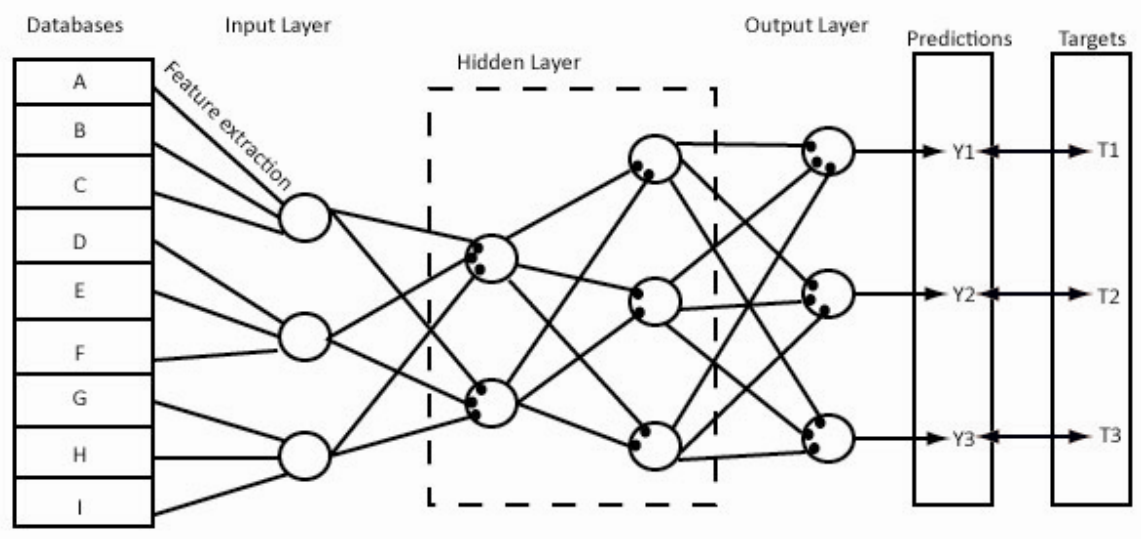


Figure 1: Schematic example of an Artificial Neural Network. The different databases are represented by the alphabets A – I. Open circles represent the nodes in the network. Small filled in circles represent the weights at the node junctions. Y1, Y2 and Y3 represent the prediction vectors. T1, T2 and T3 represent the targets used for training the network.

Unsupervised Learning

In unsupervised learning, the target is unknown; such as a previously unknown problem with a chemical, contamination, or event. Here the network attempts to discover an underlying pattern or trend in the input data alone and reorganizes itself accordingly. For unsupervised learning, we only need to know the characteristics of the inputs resulting from the feature extraction step. The resultant map of an unsupervised learning process shows the relationship between the input parameters. A set of features (or processes) related to each are organized into a map related to the position of the excited neurons (nodes). The position of the excited neurons within the network is then labeled with the known properties of the extracted feature creating what is known as the "top-map". The labels can be chosen according to our knowledge of the features such as food products, ingredients, chemicals, toxicity, funding, etc. The top-map describes

clusters of indicators for potential problems. Because the unsupervised network has no targets to relate the independent variables to, some post processing is required once the patterns are realized. In some cases, the target will be self-evident such as a chemical consistently present in several products that are organized into a map and related to an impending event. In other cases, the information gained from the unsupervised network will be compared to knowledge gained from the supervised network in order to efficiently identify the potential targets. Predictions from the unsupervised network will need to be validated in the field. For example, in the case of a potential contamination, facility inspections can be used to determine the veracity of our prediction. The new target information obtained from the inspection and the relationship between the features obtained from the unsupervised network will be used as a Library to update the supervised network (memory correction mode). This way the supervised network is able to gain new "knowledge" that can be used in future predictions. A Kohonen Network with a competitive learning strategy can be implemented for the unsupervised learning network. Similar to the supervised learning, the exact topology of the network will be determined experimentally.

Resources - *Data sources*

The initial design of SiDS will use data sources currently available to FDA. These data sources include those listed in Table 1. Additional databases (e.g., NIH funding, economic market data, media reports) can then be incorporated depending on target of interest. Traditionally, one of the concerns about using neural networks has been the use of a "black-box" structure for the hidden layers. Typically such concerns regard how to extract knowledge from the black-box and understand the relationships between predictor variables, and targets. Various algorithms have been developed as a solution to these concerns. Algorithms such as (TREPAN) are capable of extracting knowledge from neural networks. Such algorithms can be used to extract a set of rules that predict where in the data space the neural network may perform poorly. This will indicate where new data should be collected and used to improve the predictive capacity and generalization ability of the network.

Table I

CFSAN	CORE	CVM	CDC	POISON CONTROL
FACTS	PROMED	Consumer Complaints	PulseNet	Poison control center database
OASIS	HEALTH MAP	Complaints from Veterinary officers		
MARCS	Open Sources			
FURLS	EpiEx			
MINTEL	Post-response database			
GLADSON				
NHANES				
Nielsen Market Data				
Recall Database				
Reportable Foods Registry				
CAERS				
CERES				

Resources – *Personnel*

The pilot phase of this project can be started with two FTE's who will develop the software application and tap into the expertise of various subject matter experts from the different offices within CFSAN. Any available additional personnel could be incorporated to increase the progress speed of the project. Once the pilot phase is completed, the two FTE's will continue with monitoring the system and coordinating with the different offices as information is gained from the system.

Resources – *Computer and Software*

While ANN's can be computer resource intensive depending on the complexity of the topology of the network particularly during the learning/training phase of the network, the specifications of current scientific computing workstations at CFSAN may prove adequate in developing and training the network. There are various commercial software packages that can be used in developing ANN's. Under HHS's license to SAS, FDA has access to the SAS Enterprise Miner which can be used to build artificial neural networks. Currently approximately 5 licenses are in use at FDA with one in use at OFAS.

CERES

The Chemical Evaluation and Risk Estimation System (CERES) project under development in FDA's Center for Food Safety and Applied Nutrition aims at establishing a sustainable data management and storage system that will provide decision support tools for both pre-market and post-market safety assessments of food additives and food contact substances as well as for potential contamination issues. The development of CERES will provide a single unified data repository that compiles available information on a substance, including: chemical structures and properties, regulation records, toxicity studies, and other biological screening assays. In cases where no information is available for a particular substance, CERES provides tools to identify potential safety concerns by applying mode of action-driven QSAR prediction models as well as to identify and analyze data on structural and biological analogs (read-across). The knowledge-base consists of modules of structural alerts and

chemical class-driven QSAR models based on biological rules. The structural alerts/chemical classes reflect the categories of threshold of toxicological concerns (TTC), whose threshold values will be stratified across multiple toxicity endpoints allowing for the pre- and post-market evaluation of food additives under a TTC paradigm. Knowledge derived from this evaluation can be used to eliminate unnecessary toxicity testing or to identify new safety concerns as new exposure and toxicity data are incorporated into the model.

Appendix E: Example of a Signal Report Entry Form in Traction to be used by CFSAN staff